

Fig. 1.—Oxygen exchange vs. hydrolysis in the basic hydrolysis of substituted methyl benzoates in $\frac{1}{3}$ dioxane- $\frac{2}{3}$ H_2O at $24.7 \pm 0.1^\circ$: \circ , $p\text{-NH}_2$; \bullet , $p\text{-CH}_3$; \circ , $p\text{-H}$; \bullet , $p\text{-Cl}$; \bullet , $p\text{-NO}_2$.

rate constants. The effect of structural changes in the group R on this partitioning of the tetrahedral intermediate would be expected to be nil since any electronic effect on the breaking of the carbon-methoxide oxygen bond should be exactly the same as its effect on the breaking of the very similar carbon-hydroxide oxygen bond. The present experimental results test this prediction and show that the prediction is totally incorrect. The obvious reason for the inaccuracy of the prediction is that the mechanism given above is incorrect.

Experimental

Materials.—Water, dioxane and the standard solutions were prepared as described in the previous paper.²

Oxygen-18 Labeled Compounds.—Methyl benzoate- $\text{carbonyl-}^{18}\text{O}$, methyl p -nitrobenzoate- $\text{carbonyl-}^{18}\text{O}$, methyl p -toluate- $\text{carbonyl-}^{18}\text{O}$ and methyl p -chlorobenzoate- $\text{carbonyl-}^{18}\text{O}$ were prepared from the corresponding oxygen-18 labeled acids by converting them to the acid chloride with thionyl chloride and treating the acid chloride with excess methanol. The labeled carboxylic acids were prepared by treatment of the corresponding acid chloride with H_2^{18}O (Weizmann Institute of Science, 1.8% ^{18}O). The esters had essentially the same physical constants as the unlabeled materials reported in the literature.

Methyl p -aminobenzoate- $\text{carbonyl-}^{18}\text{O}$ was prepared directly from the unlabeled acid by the following procedure. p -Aminobenzoic acid (Eastman Kodak Co.; 15.1 g.) was placed in 60 ml. of 17% hydrochloric acid. The water and excess hydrochloric acid were removed by heating under vacuum. The amine hydrochloride was dissolved in 200 ml. of methanol (Fisher A.C.S.), 5 ml. of H_2^{18}O (Weizmann Institute, 1.8% ^{18}O); 4 drops of concentrated sulfuric acid was added and the solution was refluxed for 60 hours. The acid was neutralized by adding 400 ml. of saturated sodium bicarbonate solution and the ester was extracted from the aqueous phase by three 100-ml. portions of methylene chloride. The methylene chloride was removed under vacuum, and the ester was recrystallized twice from methanol-water and vacuum dried; m.p. 111° . This synthesis depends on the fact that under these conditions two equilibria (acid \rightleftharpoons ester and acid \rightleftharpoons acid- ^{18}O)⁷ are completely operative and

that the methanol \rightleftharpoons methanol- ^{18}O equilibrium is not operative.⁸

Kinetics of Hydrolysis.—The solvent for these hydrolyses, $\frac{1}{3}$ dioxane- $\frac{2}{3}$ water, was prepared by diluting one volume of dioxane with two volumes of water. For the hydrolysis of methyl benzoate, methyl p -aminobenzoate and methyl toluate, which have reasonable solubility in this solvent, the rate was determined by acid-base titration. The rates of hydrolysis of methyl p -chlorobenzoate and methyl p -nitrobenzoate, which are quite insoluble in this solvent, were determined spectrophotometrically using a Beckman DK-2 spectrophotometer. In all cases the second-order rate constants were obtained by utilizing the integrated second-order rate equation.

Oxygen Exchange.—Samples of the methyl benzoates enriched in $\text{carbonyl-}^{18}\text{O}$ were partially hydrolyzed under conditions approximately the same as those used in the hydrolytic experiments. After the appropriate time interval, the unreacted labeled ester was recovered as follows. The reaction was quenched with a phosphate buffer of pH 7.0 and the unreacted ester was recovered from the aqueous phase by six methylene chloride extractions. The methylene chloride was removed, and the recovered esters purified by recrystallization from methanol-water solution until the melting point agreed closely with the literature value. The oxygen-18 content of the ester samples was determined by converting them to carbon dioxide according to the method described in the previous paper² and analyzing the carbon dioxide samples for their oxygen-18 content with a Consolidated-Nier model 21-201 isotope-ratio mass spectrometer.

Results

The second-order rate constants for the alkaline hydrolysis of the five substituted methyl benzoates are listed in Table I. A Hammett plot of the

TABLE I
RATE CONSTANTS FOR THE BASIC HYDROLYSIS OF SUBSTITUTED METHYL BENZOATES^a

Substituent	$k_h \times 10^3$, l./mole sec.
$p\text{-NH}_2$	1.14 ± 0.04^b
$p\text{-CH}_3$	$11.1 \pm .2$
$p\text{-H}^c$	$23.2 \pm .4$
$p\text{-Cl}$	68 ± 2
$p\text{-NO}_2$	700 ± 20

^a Solvent: $\frac{1}{3}$ dioxane- $\frac{2}{3}$ water; temperature $24.7 \pm 0.1^\circ$. ^b Average deviation for repeated runs.

kinetic data shows a precise linear relationship with a slope (ρ) of $+1.93$. The value of ρ for the saponification of a series of substituted ethyl benzoates has been shown to be solvent dependent⁹ and thus the value obtained in $\frac{1}{3}$ dioxane-water differs somewhat from that usually quoted in the literature (ρ 2.50), which refers to 87.83% ethanol-water.⁶ However, in an acetone-water solvent containing 700 ml. of water per liter, a ρ of 1.99 has been obtained for the saponification of a series of ethyl benzoates, in good agreement with the present results.⁹

The oxygen exchange data for the five substituted methyl benzoates are plotted in Fig. 1 and collected in Table II.

It is seen that the partitioning of the tetrahedral addition intermediate, as measured by the ratio k_h/k_{ex} , is indeed a function of the substituent in the p -position of the methyl benzoate. Furthermore, the substituent effect is a substantial one. Thus the prediction based on eq. 1 is not fulfilled.

(7) M. L. Bender, R. R. Stone and R. S. Dewey, *J. Am. Chem. Soc.*, **78**, 318 (1956).

(8) I. Dostrovsky and F. S. Klein, *J. Chem. Soc.*, 4401 (1955).

(9) E. Tommila, A. Nurro, R. Muren, S. Merenheimo and E. Vuorinen, *Suomen Kem.*, **B32**, 115 (1959).

TABLE II
OXYGEN EXCHANGE ACCOMPANYING BASIC HYDROLYSIS
SUBSTITUTED METHYL BENZOATES^a

Substituent	Sigma ^b	k_h/k_{ex} ^c
<i>p</i> -NH ₂	-0.66	30 ± 4
<i>p</i> -CH ₃	- .170	11 ± 2
<i>p</i> -H ⁵	.0	5.2 ± 0.8
<i>p</i> -Cl	+ .226	6.3 ± 1.0
<i>p</i> -NO ₂	+ .778	2.8 ± 0.3

^a Solvent 1/3 dioxane-2/3 water; temperature 24.7 ± 0.1°. ^b H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953). ^c Errors are maximum deviations taken from the plot of the experimental data.

Figure 2 shows a Hammett plot of the oxygen exchange data to determine the susceptibility of the partitioning of the tetrahedral addition intermediate to polar substituent effects in the acyl group. The value of ρ obtained from the slope of this plot is -0.70, with only the value of the unsubstituted compound falling off the line.

Discussion

As mentioned in the Introduction, the mechanism given in eq. 1 leads to an expression for the second-order rate of hydrolysis, k_h , equal to $k_1/((k_2/k_3) + 1)$. Although the hydrolytic rate constant is a complex constant there are several sets of circumstances under which it will reduce to a single rate constant and will therefore conform to a simple Hammett relationship. If, for example, the value of k_2/k_3 is independent of substituent, the denominator of the above equation will be a constant and relative rates upon substitution will be given by

$$\log (k_h/k_h^0) \cong \log (k_1/k_1^0) + \text{constant} \quad (2)$$

and the value of the ρ measured for this reaction will thus be a measure of the addition step, k_1 . Of course it is seen from Table II that $k_2/k_3 (= 1/2 k_{ex}/k_h)$ is not constant. However the values of k_2/k_3 , calculated on this basis, are all less than one and thus $k_h \cong k_1$. Consequently only a very small fraction of the 600-fold change in k_h seen in Table I can be accounted for by a change in the value of k_2/k_3 and the variation in k_h must be the result of large changes in k_1 . Therefore the linearity observed in the Hammett plot of k_h is due to the fact that the partitioning of the intermediate does not influence the relative rates greatly, and thus eq. 2 is approximately correct. This situation is therefore different from the hydrolysis of *p*-substituted acetanilides,² and also different from the formation of oximes from substituted benzophenones,¹⁰ and the reactions of substituted benzaldehydes with *n*-butylamine¹¹ and semicarbazide^{12,13} where non-linear Hammett plots have been found. In these latter cases the same kind of stepwise processes occur as in the methyl benzoate hydrolysis, but in these reactions presumably k_2/k_3 is much greater than one and the effect of substituents conforms to the complicated

(10) J. D. Dickinson and C. Eaborn, *J. Chem. Soc.*, 3036 (1959).

(11) G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *J. Am. Chem. Soc.*, **80**, 1254 (1958).

(12) D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, **23**, 752 (1958).

(13) B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

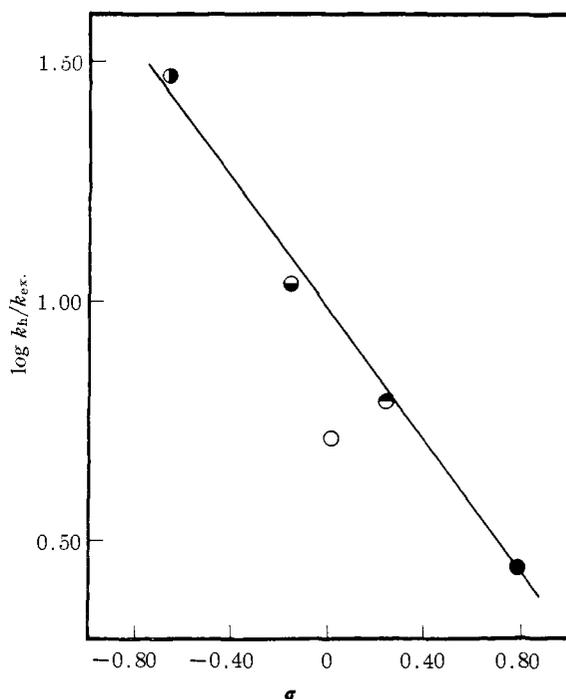


Fig. 2.—Hammett plot of the oxygen exchange data for the basic hydrolysis of substituted methyl benzoates in 1/3 dioxane-2/3 water at 24.7 ± 0.1°: ●, *p*-NH₂; ○, *p*-CH₃; ○, *p*-H; ●, *p*-Cl; ●, *p*-NO₂.

non-linear Hammett relationship described in detail by Noyce, *et al.*¹²

As pointed out earlier, the experimentally determined ratio of the rate constants of hydrolysis to exchange, k_h/k_{ex} , can be shown to be proportional to the ratio of the partitioning of the tetrahedral intermediate, k_3/k_2 , by applying the steady state approximation to eq. 1. The ratio k_h/k_{ex} has been shown to be a function of the structural effects of the leaving group.¹⁴ These effects have been rationalized successfully in terms of the partitioning of the tetrahedral intermediate in eq. 1. In the present experiments, however, the ratio k_h/k_{ex} has been shown to be a function of the substituent on the *p*-position of the *carboxylic acid moiety*, a situation that cannot be explained in terms of the partitioning predicted by eq. 1.

The central assumption involved in the mechanism shown in eq. 1 is that the proton transfers to and from the intermediate are much faster than the breakdown of the intermediate to either reactant or product. If, however, the proton transfers (k_4 and k_5) must be taken into account, the kinetic expression for k_h/k_{ex} becomes

$$k_h/k_{ex} = 2(k_3/k_4 + k_3^2/k_2k_4 + k_3/k_2)^{15,16} \quad (3)$$

(14) M. I. Bender, *Chem. Revs.*, **60**, 53 (1960).

(15) Equation 3 assumes as in eq. 1 that the proton transfer from one oxygen atom to the other in the tetrahedral intermediate occurs in two steps, the first being a donation of a proton from the solvent to give a neutral species, RC(OH)₂OR, and the second being the removal of a proton from the neutral species by a hydroxide ion (*vide infra*). The rate constant, k_5 , does not appear in eq. 3: it cancels in the derivation of eq. 3 due to the symmetry of the system.

(16) A. Moffat and H. Hunt, *J. Am. Chem. Soc.*, **81**, 2082 (1959), suggested that proton transfers in the intermediate were significant and derived essentially this equation.

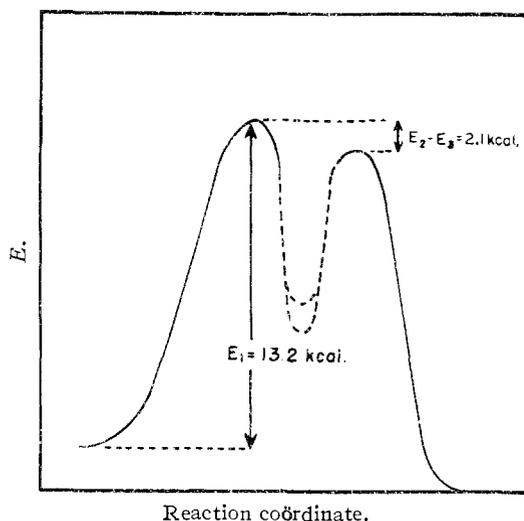


Fig. 3.—The hydrolysis of ethyl benzoate.

instead of the simple expression $k_h/k_{ex} = 2k_3/k_2$ derived for the case in which proton transfers were considered to be kinetically insignificant. Equation 3 of course reduces to the latter expression if k_4 is much larger than k_3 . Equation 3 can account for the substituent effect on the values of k_h/k_{ex} as may be seen from an alternate form of eq. 3.

$$k_h/k_{ex} = 2k_3/k_4(1 + k_3/k_2) + 2k_3/k_2 \quad (4)$$

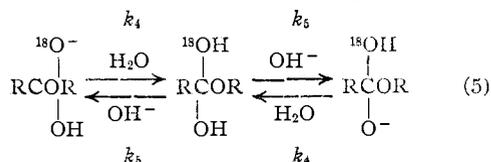
Assuming that the value of k_3/k_2 is independent of substituent, the value of k_h/k_{ex} will decrease as the substituent is changed from p -NH₂ to p -NO₂ if k_3/k_4 decreases. A decrease in k_3/k_4 for this change in substituents would be expected on the following grounds. Both k_3 and k_4 should decrease upon the introduction of an electronegative substituent, but the decrease in k_3 should be larger than that in k_4 since the bond broken in the k_3 step is situated on the side chain one atom closer to the benzene ring than the bond broken in the k_4 step.

Assuming that eq. 3 correctly describes the ratio k_h/k_{ex} , one may calculate the range of values permitted for k_3/k_4 . That is, if $k_3/k_4 = 0$, the value of $2k_3/k_2$ equals the value of k_h/k_{ex} . As k_3/k_4 should be smallest for the p -NO₂ substituent, the value of k_h/k_{ex} for the p -NO₂ substituent, 2.8, represents the maximum value permitted by eq. 3 for $2k_3/k_2$. Using 1.4 as the constant value of k_3/k_2 and the observed values of k_h/k_{ex} , one can calculate using eq. 3 the *minimum* values allowed for k_3/k_4 , obtaining for the substituents p -NO₂, p -Cl, p -H, p -CH₃ and p -NH₂ the values 0.0, 0.8, 0.5, 1.7 and 5.6, respectively. Allowing k_3/k_2 to approach zero, the *maximum* values permitted by eq. 3 for k_3/k_4 are 1.4, 3.2, 2.6, 5.6 and 15, respectively. For a given substituent, the permitted values of k_3/k_4 vary by a factor of five or less. The permitted values of k_3/k_4 for the p -NO₂ substituent vary by a much larger factor, but this is to be expected as the value of k_h/k_{ex} for the p -NO₂ substituent was used as a boundary condition. The range of values of the ratio k_3/k_4 for the substituents other than p -NO₂ indicate that the rate constant for the proton transfer in the intermediate, k_4 , is of the same order of magnitude as the value of the

rate constant for decomposition of the intermediate to products, k_3 . This is a surprising result and deserves additional comment.

An estimate of the kinetic relevance of the proton transfers to and from the tetrahedral intermediate, k_4 , as compared to the decomposition of the intermediate to products, k_3 , will be attempted. First, let us make an estimate of the value of k_3 . From the dependence of the ratio k_h/k_{ex} for the saponification of ethyl benzoate on temperature¹⁷ (the ratio increases with decreasing temperature), and applying the now questionable assumption that k_4 is kinetically insignificant, one can calculate the following activation energies: E_h , 12.9; E_{ex} , 14.9; E_1 , 13.2; $E_3 - E_2$, -2.1 kcal./mole.¹⁷ From these data one can see that the formation of the tetrahedral intermediate, k_1 , is the kinetically important step (Fig. 3). Unfortunately the two pieces of experimental evidence do not allow one to specify all three rate constants even in this oversimplified picture. Still unknown is the depth of the valley in the diagram, as indicated by the dotted line; that is, the absolute values of the activation energies of either process concerned with the breakdown of the tetrahedral intermediate are unknown. Since E_1 is 13.2 kcal./mole and since the barrier to E_3 is 2.1 kcal./mole lower than the E_2 barrier, one can say that the absolute value of E_3 is most certainly below 11 kcal./mole. In addition it is reasonable on chemical grounds to assume that the floor of the valley, the energy of the intermediate, is considerably above that of the ground state of the ester. The largest estimate of the activation energy E_3 that might be made is of the order of 6 kcal./mole. Although this estimate is open to considerable criticism, it is difficult to conceive how the value of E_3 can be *higher* than that given above. On the basis of the assumed activation energy of 6 kcal./mole, it can be calculated that a *lower* limit on the rate constant for the k_3 step is in the range of 10^9 sec.⁻¹.¹⁸

Now let us consider what values the kinetic parameters associated with the proton transfers in the tetrahedral intermediate might assume. The most probable proton transfer process is the following intermolecular process, as in eq. 1.



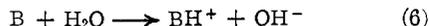
The proton transfers, k_4 and k_5 , involve protonation of the anionic intermediate by water to form the neutral species followed by abstraction of a proton from the neutral species by hydroxide ion to form the complementary anionic intermediate. This process may be shown to lead to eq. 3 by a steady state treatment; because of the symmetrical

(17) M. J. Bender, R. D. Ginger and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1958).

(18) This calculation is based on the equation, $k = 10^{13} e^{-\Delta E/RT}$ for this unimolecular decomposition reaction. It is assumed that since we are dealing with a relatively unstable intermediate, the transition state of the reaction will resemble the intermediate ground state (see G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955)) and thus the assumption of a normal pre-exponential term is valid.

nature of the system the rate constant k_5 cancels in the derivation of the expression for k_h/k_{ex} .

The rate constants for the reaction



have been determined experimentally for a large number of oxy-anions and nitrogen bases. The rate constants of these reactions are to a first approximation directly proportional to the basicities of B, varying from 4×10^9 l./mole sec. for the reaction $OH^- + H_2O$ to 4×10^{-7} l./mole sec. for $H_2O + H_2O$.¹⁹ If the pK_a of the tetrahedral intermediate is of the same order of magnitude as that for formaldehyde hydrate (5.1×10^{-14}),²⁰ one would expect that the value of the rate constant k_4 might be of the order of 10^8 l./mole sec. or 10^9 sec.⁻¹.²¹ Since it has been shown previously that one need not consider the proton transfer in step k_5 because of the symmetry of the system, a consideration of k_4 alone leads to a proper kinetic assessment of the proton transfer possibilities in the tetrahedral intermediate. This consideration indicates that proton transfer, $k_4 \cong 10^9$ sec.⁻¹, is of the same order of magnitude as decomposition to products, $k_3 \cong 10^9$ sec.⁻¹ (a lower limit). These estimates account for the values of k_3 and k_4 calcu-

(19) C. Meiboom, *J. Chem. Phys.*, **34**, 375 (1961); M. Eigen, *Z. Elektrochem.*, **64**, 122 (1960); M. Eigen, G. G. Hammes and K. Kustin, *J. Am. Chem. Soc.*, **82**, 3482 (1960); M. Eigen and L. DeMaeyer, *Z. Elektrochem.*, **59**, 986 (1955).

(20) R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2983 (1960). Formaldehyde hydrate is the best analog of the intermediate at the present time.

(21) M. Eigen, *Disc. Faraday Soc.*, **17**, 204 (1954).

lated from the experimental data above, which are also of the same order of magnitude.

These crude considerations point to the possibility that proton transfer, k_4 , may be kinetically significant with respect to decomposition to products, k_3 . Therefore one cannot assume in the mechanism for concurrent hydrolysis and isotopic oxygen exchange that the proton transfers in the tetrahedral intermediate are kinetically insignificant (as was done before the days in which measurements of proton transfers were put on a sound experimental basis), but rather should assume that the proton transfer step may play an important part of the over-all mechanism. Certainly in the present instance, the striking substituent effects cannot be explained in terms of the earlier mechanism in which proton transfers were neglected, but can be explained readily if their presence is taken into account. A possible result of the importance of proton transfer in reactions of the tetrahedral intermediate is that deuterium isotope effects associated with these proton transfers will be measurable. Preliminary evidence to this effect has been obtained in these laboratories and is being pursued at the present time.

Acknowledgments.—The authors acknowledge with pleasure valuable discussions with Dr. G. A. Hamilton and Dr. R. G. Pearson, and wish to express their appreciation to Dr. H. Taube of the University of Chicago through whose courtesy the mass-spectrometer under AEC Contract At(11-1)-92 was made available.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL., AND NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

The Concurrent Alkaline Hydrolysis and Isotopic Oxygen Exchange of Several Alkyl Benzoates and Lactones^{1,2}

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RECEIVED MAY 13, 1961

The kinetics of the concurrent alkaline hydrolysis and isotopic oxygen exchange of methyl benzoate, *p*-chlorobenzyl benzoate, *p*-methoxybenzyl benzoate, phthalide and γ -butyrolactone have been determined. Only in the hydrolysis of methyl benzoate has concurrent oxygen exchange been found. In the other hydrolyses, the exchange reaction is not present within experimental error. A lower limit to the ratio k_h/k_{ex} in the latter reactions has been calculated. The surprising lack of oxygen exchange in the hydrolysis of the benzyl benzoates, as contrasted to that of the kinetically similar methyl benzoate, is attributed to the preferential partitioning of the tetrahedral intermediate to products to relieve steric strain in the intermediate caused by the bulky benzyloxy group.

Introduction

Concurrent carbonyl oxygen exchange and hydrolysis have been demonstrated in the hydrolyses of a number of benzoate esters including ethyl, isopropyl and *t*-butyl benzoates.⁴ This concurrent hydrolysis and exchange has been interpreted in terms of the partitioning of an unstable tetrahedral addition intermediate of the form $RC(OH)_2$ -

OR. The magnitude of the carbonyl oxygen exchange which accompanies hydrolytic reactions of carboxylic acid derivatives permits a description of the partitioning of the addition intermediate into reactants and products. In the previous paper,² for example, the effect of *p*-substituents on the partitioning of the tetrahedral intermediate in the alkaline hydrolysis of a series of *p*-substituted methyl benzoates was investigated. The results of that investigation led to the postulation that the proton transfers in the tetrahedral intermediate, which must take place to make the two oxygen atoms equivalent to one another (and thus which must take place for exchange to occur) are kinetically significant with respect to the decomposition

(1) This research was supported by grants from the National Science Foundation and the U. S. Atomic Energy Commission.

(2) Paper XI in the series, Intermediates in the Reactions of Carboxylic Acid Derivatives. Previous paper, M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4189 (1961).

(3) (a) Alfred P. Sloan Foundation Research Fellow; (b) Department of Chemistry, Northwestern University, Evanston, Ill.

(4) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).